

## HIGHLIGHT

## Gene therapy in advanced metachromatic leukodystrophy: tempering expectations

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Recently Zhang et al. (2024) published their study entitled “Lentivirus-modified hematopoietic stem cell gene therapy for advanced symptomatic juvenile metachromatic leukodystrophy: A long-term follow-up pilot study.” The authors present three metachromatic leukodystrophy (MLD) patients treated with gene therapy and claim stabilization or even improvement, despite advanced symptomatic disease stage. The metachromatic leukodystrophy initiative (MLDi) (Schoenmakers et al., 2022), an international collaborative network and registry for MLD, urges caution in interpreting these results, as the evidence raises several critical concerns. These claims risk fostering false hope among MLD patients and their families, particularly given the significant gaps in the data provided (Fig. 1).

The authors suggest beneficial outcomes of gene therapy in advanced MLD. Two of the three patients (MLD01 and MLD02) presented were already clearly affected at the time of treatment, exhibiting symptoms indicating advanced disease, such as dysphagia, urinary incontinence, and loss of walking. Based on an increased functional independence measure (FIM) score and/or gross motor function classification for MLD (GMFC-MLD) the authors suggest considerable improvement, e.g., walking with quality and performance normal for age. However, in addition to this composite and crude clinical score, detailed clinical information about, e.g., cognition,

gross- and fine motor function, eating and drinking ability, and speech is necessary to comprehensively assess the clinical status of the patients and substantiate the claim of neurological improvement. The authors interpret improved arylsulfatase A (ARSA) activity as a treatment benefit. This biochemical characteristic implies technical treatment success, but should not be confused with clinical benefit.

The third treated patient (MLD03) was diagnosed pre-symptomatically at age 1.6 years following family screening and cannot be considered an advanced symptomatic MLD patient. The near-normal Magnetic Resonance Imaging (MRI) at diagnosis and maximum clinical scores advocate for an early disease stage at baseline. The described muscle weakness may be explained by peripheral neuropathy, but no information on electro-neurophysiological tests is given. It is common that peripheral neuropathy appears early in the disease course of MLD and may even be present years before the central manifestation of the disease (Beerepoot et al., 2019). Treatment before developing central nervous system symptoms is generally followed by good clinical outcomes (Boucher et al., 2015; Fumagalli et al., 2022; Groeschel et al., 2016; van Rappard et al., 2016).

The article lacks crucial details, such as detailed inclusion criteria defining “advanced disease status,” the total number of treated patients, and outcomes of other treated patients. This information is essential to understand the efficacy and safety of a new treatment. Moreover, the reported *in vivo* vector copy numbers appear suboptimal for achieving enzyme activity over-expression necessary for significant clinical benefit.

Previous research emphasizes that severe nervous system damage is irreversible, and full recovery of lost neurological function is unlikely (Fumagalli et al., 2021). The impressive improvement from GMFC-MLD level 4 to level 0 in MLD01 is questionable, particularly considering the extensive damage on baseline MRI. Regaining normal walking in quality and performance (GMFC-MLD 0) after complete loss of upright mobility (GMFC-MLD 4) is very unlikely if caused by neurological damage (cerebellar, spasticity, or neuropathy). This has never been observed in previous *ex vivo* gene therapy trials for MLD (Fumagalli et al., 2022), highlighting the need for caution in interpreting these results.

Several studies reporting outcomes of allogeneic hematopoietic stem cell transplantation have shown the importance of treating before severe symptoms occur (Boucher et al., 2015; Groeschel et al., 2016; van Rappard et al., 2016). The conditioning regimen with chemotherapy may even trigger deterioration in advanced disease stages (Beschle et al., 2020). The past years of experience with the use of atidarsagene autotemcel (Libmeldy™), the authorized lentiviral gene therapy for MLD in the European Union and the USA, have confirmed this. When

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In response to the publication of Zhang et al. entitled *Lentivirus-modified hematopoietic stem cell gene therapy for advanced symptomatic juvenile metachromatic leukodystrophy: A long-term follow-up pilot study* published in *Protein & Cell* on 25 June 2024.

### Main points of criticism



Claims of efficacy while detailed clinical information is lacking



No definition of advanced disease status



All previous research emphasizes the importance of early treatment



Risk of creating false hope among patients and families



An expert collaborative network and disease registry for metachromatic leukodystrophy

**Figure 1.** Critical response to the publication of Zhang et al. regarding gene therapy in advanced MLD.

patients are too advanced, gene therapy is not beneficial (Fumagalli et al., 2022). During the trial of Fumagalli et al. (2022), the eligibility criteria were even amended to avoid inclusion of severely affected juvenile patients. Nowadays, the eligibility criteria adopted by experts include the ability to walk without support (GMFC-MLD < 2) and substantial residual cognitive function (total intelligence quotient  $\geq$  85) (Schoenmakers et al., 2024). We acknowledge that treatment decisions for borderline patients are difficult. Especially late-juvenile and adult MLD patients can present with an insidious onset and slow decline. Careful consideration of potential risks associated with treatment, along with the fact that the beneficial effects of autologous and allogeneic stem cell therapy can be expected after 6–12 months, is essential in treatment decisions.

To conclude, the message portrayed in the study of Zhang et al. is not in line with current best practices for the management of MLD patients (Fumagalli et al., 2022; Laugwitz et al., 2024b) and provides insufficient detail to judge efficacy and safety of this new and invasive treatment. We acknowledge the significant unmet need for treatments for late-juvenile and adult MLD, as well as for advanced disease stages. Fortunately, atidarsagene autotemcel is currently being investigated in early-symptomatic late-juvenile patients (NCT04283227). Future treatments in advanced disease stages will at best be able to modify the disease course, but not to achieve a cure or significant improvement. To identify patients in time to guarantee successful treatment, newborn screening is the best option (Laugwitz et al., 2024b, 2024a).

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## Conflict of interest

All authors are part of the MLD initiative. L.A.: Consultant to Biogen, Takeda Pharmaceuticals, Orchard Therapeutics is a site sub-investigator for the Takeda trial, and serves on the scientific advisory board of Cure MLD and MLD Foundation. A.B.: Site sub-investigator for the Takeda SHP611 trial and received traveling

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## Authors' contributions

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